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# EFFECT OF A METAL SALT ON THIIRANATION OF 2'-ADAMANTYLIDENE-9-BENZONORBORNENYLIDENE WITH 4,4'-DITHIODIMORPHOLINE AND ACETIC ANHYDRIDE

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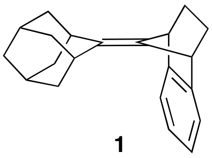
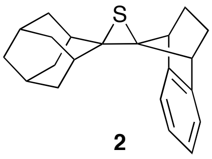
**Abstract** – Using a solution of a metal salt, it was possible to decrease the quantity of $Ac_2O$ used in the thiiranation of 2'-adamantylidene-9-benzonorbornenylidene **1** with 4,4'-dithiodimorpholine **4** and $Ac_2O$. Thiiranation in a 0.1 M $Et_2O$ solution of $LiClO_4$ at −15 °C afforded thiiranes **2** and **3** in moderate yields without the decomposition of the thermally less stable **3**.

Thiiranes, as well as oxiranes and aziridines, can act as key intermediates in the syntheses of functional materials and biologically active compounds. Thus far, numerous methods, such as two-step synthesis from alkenes through oxiranes (a conventional laboratory method), for synthesizing thiiranes have been reported.[1] When using two-step synthesis, undesired polymerization of the resulting thiiranes occured frequently.[2] On the other hand, thiiranation of alkenes (episulfidation), i.e., direct synthesis of thiiranes from alkenes, is less common than oxiranation (epoxidation) and aziridination of alkenes.[3] There have been cases in which problems, such as the polymerization and decomposition of the resulting thiiranes, limitations of the alkenes used, and difficulty in synthesizing a sulfurating reagent, were faced during the thiiranation. Development of a new method is required to overcome these problems. Recently, we indicated the possibility of using 2'-adamantylidene-9-benzonorbornenylidene **1**, which acts as a model alkene for investigating thiiranation conditions.[4] Until now, we investigated two novel thiiranation methods with 4,4'-oligothiodimorpholines from the results of both thiiranation of **1** to the corresponding thiirane **2** and **3**, and the decomposition of **3** to **1** and **2**.[5,6] Thiirane **3** is thermally less stable than **2**; thus, the reaction of **3** at its C–S bond tends to produce **3** together with **1**. As a result, the method with 4,4'-dithiodimorpholine **4**, a commercially available, inexpensive vulcanizing agent, in $Ac_2O$ at −15 °C was found to provide the best results.[6] Although the thiiranation proceeded with retention of the configuration of the starting alkene, removal of excess $Ac_2O$ from the reaction mixture by either vacuum distillation at −15 °C or hydrolysis with LiOH restricted the use of alkenes. A method of decreasing the quantity of $Ac_2O$ used must be found. Here, we report the effect of a metal salt on the thiiranation of **1** with **4** and $Ac_2O$.


**1**



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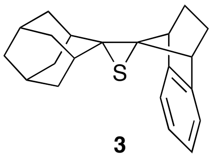
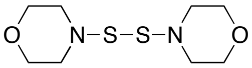


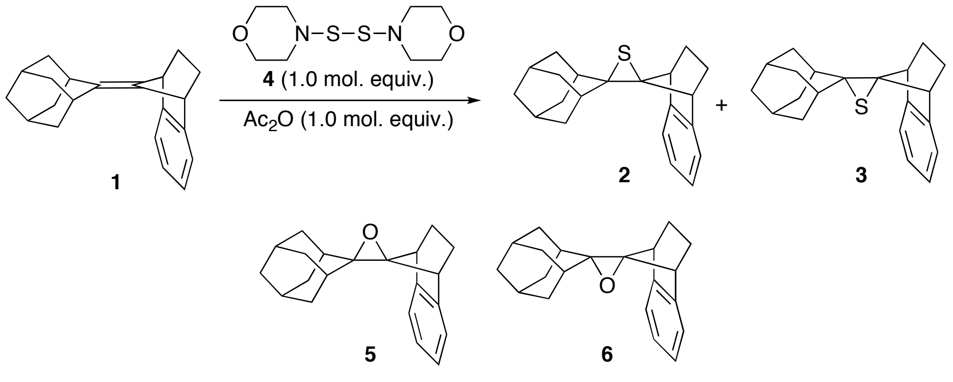
**3**



**4**

$LiClO_4$ is highly soluble in many organic solvents, such as EtOH, $Et_2O$, and acetone, and is used as a weak Lewis acid in many organic reactions.[7] A highly concentrated $Et_2O$ solution of $LiClO_4$ is known to be a powerful reaction medium in organic synthesis.[8] When this solution is used in the reaction, $LiClO_4$ not only acts as a Lewis acid, but also increases the polarity of the solvent. Therefore, some reactions that usually proceed only under drastic reaction conditions can proceed smoothly in this solution even at rt. Considering these effects, thiiranation of **1** with **4** (1.0 molar equivalent) and $Ac_2O$ (1.0 molar equivalent) in solutions of metal salts were examined (Scheme 1), and the results are summarized in Table 1. Thiiranation of **1** with **4** and $Ac_2O$ in an $Et_2O$ solution of $LiClO_4$ (4.1 molar equivalent, 0.1 M) at −15 °C proceeded to give **2** and **3** in 20 and 29% yields, respectively, together with **1** in 42% yield (Entry 1). When thiiranation was performed in $CH_2Cl_2$ at rt in the absence of $LiClO_4$, a small quantity of **3** was formed together with the recovery of **1** (Entry 2).[6] In the presence of 12-crown-4, which is known to capture $Li^+$ ions efficiently,[9] **1** was recovered (Entry 3). Increasing the concentration of $LiClO_4$ in the solution tended to increase the yields of the thiiranes slightly, but formed oxirane **5** (Entries 4 and 5). In the absence of $Ac_2O$, a quantitative recovery of **1** was observed (Entry 6). These results suggest that $Ac_2O$ is activated by the action with $LiClO_4$ as a Lewis acid, and then reacts with **4** to form a true thiiranation reagent. When the solvent was changed from $Et_2O$ into AcOEt and acetone, consumption of **1** increased, but oxirane **6** was obtained in addition to **5** (Entries 7 and 8). In these cases, AcOEt and acetone, both of which have a basic carbonyl-oxygen atom, may react with $LiClO_4$ instead of $Ac_2O$, and then with **4** to form the thiiranation reagent. The oxiranes **5** and **6** must be produced by the oxidation of **1** with the perchlorate ion $ClO_4^-$.[10] The reaction of **1** with $Ac_2O$ and $LiBF_4$ in $CH_3CN$ at −15 °C proceeded to give small quantities of **2** and **3** (Entries 9 and 10). Increasing the reaction temperature to rt resulted in the formation of **2** and **3** in moderate to good yields (Entries 11−14). Using THF and AcOEt as solvent showed the progress of thiiranation, and production of **2** was greater than that of **3** (Entries 15 and 16). When LiOTf was used, the ratio of **2** to **3** decreased significantly, compared to using $LiClO_4$ and $LiBF_4$ (Entries 17 and 18). $Mg(OTf)_2$ seems to be more efficient for activating $Ac_2O$ than LiOTf (Entries 19 and 20). From the results as shown in entries 1, 10, 18, and 20, the efficiency of the reaction medium in the thiiranation of **1** seemed to increase in the order of $LiBF_4$ in $CH_3CN$ < LiOTf in $CH_2Cl_2$ < $LiClO_4$ in $Et_2O$

< Mg(OTf)$_2$ in CH$_2$Cl$_2$.



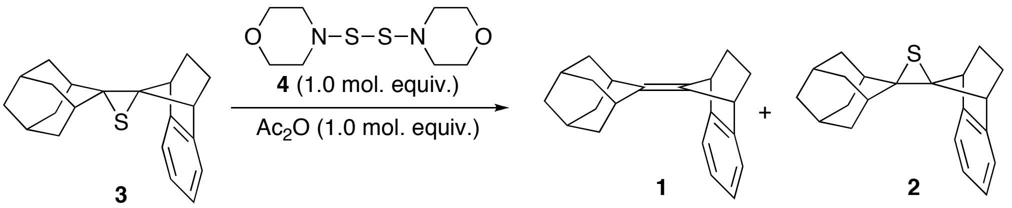
**Scheme 1**

**Table 1.** Reactions of **1** with **4** and Ac$_2$O in a Metal Salt Solution[a]

| entry | metal salt/solvent (conc., M) | conditions | yield (%) 2 | 3 | 5 | 6 | 1 |
|---|---|---|---|---|---|---|---|
| 1 | LiClO$_4$/Et$_2$O (0.1)[b] | −15 °C, 45 h | 20 | 29 | — | — | 42 |
| 2[c] | none/CH$_2$Cl$_2$ | rt, 45 h | — | 3 | — | — | 92 |
| 3 | LiClO$_4$/Et$_2$O (0.1)[b] | 12-crown-4,[d] −15 °C, 45 h | — | — | — | — | 96 |
| 4 | LiClO$_4$/Et$_2$O (1.0)[e] | −15 °C, 45 h | 31 | 30 | 8 | — | 20 |
| 5 | LiClO$_4$/Et$_2$O (2.0)[f] | −15 °C, 45 h | 35 | 40 | 7 | — | 8 |
| 6 | LiClO$_4$/Et$_2$O (2.0)[f] | −15 °C, 45 h[g] | — | — | — | — | 98 |
| 7 | LiClO$_4$/AcOEt (2.0)[f] | −15 °C, 45 h | 43 | 19 | 15 | 10 | 9 |
| 8 | LiClO$_4$/acetone (2.0)[f] | −15 °C, 45 h | 40 | 20 | 4 | 9 | 16 |
| 9 | LiBF$_4$/CH$_3$CN (2.4x10$^{-2}$)[d] | −15 °C, 168 h | 5 | 5 | — | — | 83 |
| 10 | LiBF$_4$/CH$_3$CN (0.1)[b] | −15 °C, 168 h | 3 | 4 | — | — | 87 |
| 11 | LiBF$_4$/CH$_3$CN (2.4x10$^{-3}$)[h] | rt, 120 h | 8 | 25 | — | — | 59 |
| 12 | LiBF$_4$/CH$_3$CN (2.4x10$^{-2}$)[d] | rt, 120 h | 18 | 56 | — | — | 15 |
| 13 | LiBF$_4$/CH$_3$CN (4.9x10$^{-2}$)[i] | rt, 96 h | 23 | 63 | — | — | 4 |
| 14 | LiBF$_4$/CH$_3$CN (0.1)[b] | rt, 43 h | 25 | 63 | — | — | 4 |
| 15 | LiBF$_4$/THF (0.1)[b] | rt, 120 h | 29 | 5 | — | — | 58 |
| 16 | LiBF$_4$/AcOEt (0.1)[b] | rt, 120 h | 34 | 9 | — | — | 49 |
| 17 | LiOTf/CH$_2$Cl$_2$ (2.4x10$^{-2}$)[d] | −15 °C, 72 h | 2 | 17 | — | — | 73 |
| 18 | LiOTf/CH$_2$Cl$_2$ (0.1)[b] | −15 °C, 72 h | 3 | 28 | — | — | 61 |
| 19 | Mg(OTf)$_2$/CH$_2$Cl$_2$ (2.4x10$^{-2}$)[d] | −15 °C, 72 h | 3 | 28 | — | — | 62 |
| 20 | Mg(OTf)$_2$/CH$_2$Cl$_2$ (0.1)[b] | −15 °C, 72 h | 18 | 54 | — | — | 17 |

[a] **4** (1.0 mol. equiv.), Ac$_2$O (1.0 mol. equiv.). [b] 4.1 mol. equiv. [c] Ref. 6. [d] 1.0 mol. equiv. [e] 41 mol. equiv. [f] 82 mol. equiv. [g] In the absence of Ac$_2$O. [h] 0.1 mol. equiv. [i] 2.0 mol. equiv.

Reactions of **3** with **4** (1.0 molar equivalent) and Ac$_2$O (1.0 molar equivalent) in solutions of metal salts were examined (Scheme 2), and the results are summarized in Table 2. Decomposition of **3** did not occur in the Et$_2$O solution of LiClO$_4$ (4.1 molar equivalent, 0.1 M) at −15 °C and in CH$_2$Cl$_2$ at rt (Entries 1 and 2). When the concentration of LiClO$_4$ in Et$_2$O was increased to 1.0 M, isomerization to **2** and slight decomposition to **1** were observed (Entry 3). Oxirane **5**, in addition to **1** and **2**, was obtained by the reaction in the 2.0 M solution, but the recovery of **3** increased in comparison with that in the 1.0 M solution (Entry 4). Changing Et$_2$O into AcOEt or acetone decreased both the consumption of **3** and formation of **2** (Entries 5 and 6). The reaction in the Et$_2$O solution of LiBF$_4$ (4.1 molar equivalent, 0.1 M) at −15 °C resulted in the quantitative recovery of **3**, whereas that at rt gave **1** and **2** (Entries 7 and 8). The decompositions of **3** in both the $LiClO_4$ and $LiBF_4$ solutions tended to produce **2** rather than **1**. This tendency is similar to that of the reaction of **3** with **4** (1.0 molar equivalent) and acid anhydride (1.0 molar equivalent) in $CH_2Cl_2$.[6] On the other hand, an approximately 1:1 to 1:2 mixture of **1** and **2** was obtained in the decompositions in metal-triflate solutions (Entries 9–11). From the results shown in entries 1, 7, 9, and 10, the order of ability as the reaction medium in the decomposition of **3** seemed to be LiOTf in $CH_2Cl_2 \approx Mg(OTf)_2$ in $CH_2Cl_2 < LiBF_4$ in $CH_3CN \approx LiClO_4$ in $Et_2O$. Therefore, thiiranation in the 0.1 M $Et_2O$ solution of $LiClO_4$ at −15 °C produced the best results, because the thiiranation gave **2** and **3** in moderate yields without the decomposition of the thermally less stable **3**.



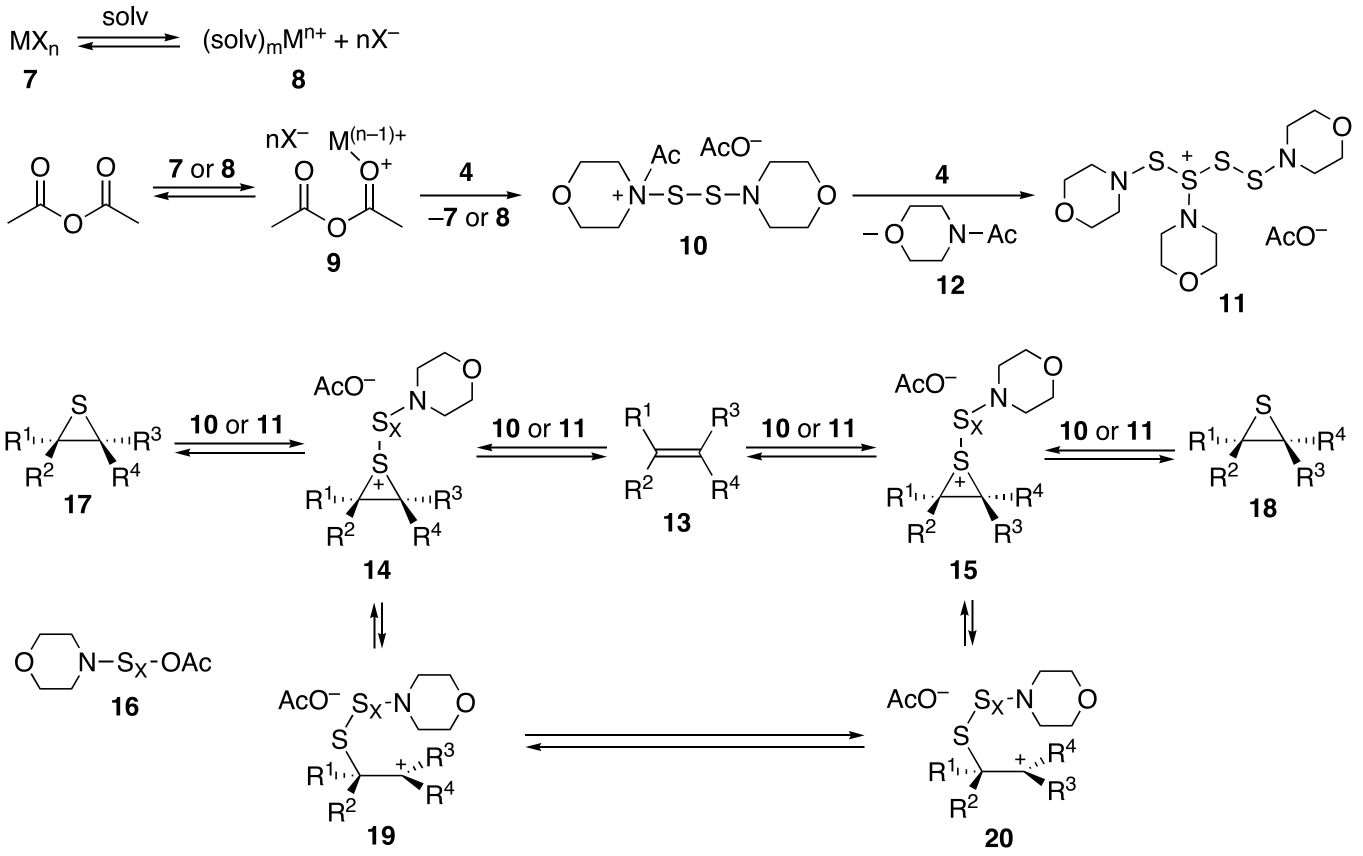
**Scheme 2**

**Table 2.** Reactions of **3** with **4** and $Ac_2O$ in a Metal Salt Solution[a]

| entry | metal salt/solvent (conc., M) | conditions | yield (%) **1** | yield (%) **2** | yield (%) **5** | yield (%) **3** |
|---|---|---|---|---|---|---|
| 1 | $LiClO_4/Et_2O$ (0.1)[b] | −15 °C, 45 h | — | — | — | 94 |
| 2[c] | none/$CH_2Cl_2$ | rt, 45 h | — | — | — | quant. |
| 3 | $LiClO_4/Et_2O$ (1.0)[d] | −15 °C, 45 h | 2 | 84 | — | 4 |
| 4 | $LiClO_4/Et_2O$ (2.0)[e] | −15 °C, 45 h | 3 | 44 | 14 | 29 |
| 5 | $LiClO_4$/AcOEt (2.0)[e] | −15 °C, 45 h | — | 18 | — | 69 |
| 6 | $LiClO_4$/acetone (2.0)[e] | −15 °C, 45 h | — | 22 | — | 71 |
| 7 | $LiBF_4/CH_3CN$ (0.1)[b] | −15 °C, 168 h | — | — | — | quant. |
| 8 | $LiBF_4/CH_3CN$ (0.1)[b] | rt, 48 h | 5 | 63 | — | 32 |
| 9 | LiOTf/$CH_2Cl_2$ (0.1)[b] | −15 °C, 168 h | 14 | 24 | — | 60 |
| 10 | $Mg(OTf)_2/CH_2Cl_2$ ($2.4x10^{-2}$)[f] | −15 °C, 168 h | 14 | 20 | — | 66 |
| 11 | $Mg(OTf)_2$ /$CH_2Cl_2$(0.1)[b] | −15 °C, 168 h | 17 | 16 | — | 67 |

[a] **4** (1.0 mol. equiv.), $Ac_2O$ (1.0 mol. equiv.). [b] 4.1 mol. equiv. [c] Ref. 6. [d] 41 mol. equiv. [e] 82 mol. equiv. [f] 1.0 mol. equiv.

A possible mechanism of the thiiranation of **1** and the decomposition of **3** is as follows. A metal salt **7** is solvated by coordination to the basic atom in the solvent to form **8**. The $M^+$ ion from **7** or **8** coordinates the carbonyl-oxygen atom in $Ac_2O$ to give ammonium salt **10**, which then reacts with **4** to form sulfonium salt **11**. The salts **10** and **11** must act as a thiiranation reagent. Reaction of **13** with **10** or **11** gives thiiranium salts **14** and **15**, which then extrude **16** to give **17** and **18**, respectively. The decomposition of **3** to **2** proceeds through the thiiranium salts **14** and **15** and carbenium salts **19** and **20**, and that to **1** is a reverse process of thiiranation. The processes among **13–15** and **17–20** are reversible, and therefore, the ratio of **1**, **2**, and **3** may be determined by both the Lewis acidity of the metal salt and the polarity of the concentrated solution of the metal salt.



Scheme 3

In summary, we studied the effect of a metal salt on the thiiranation of **1** with **4** and Ac$_2$O. As a result, the 0.1 M Et$_2$O solution of LiClO$_4$ at −15 °C was used as a reaction medium for successful thiiranation of **1**. Further work is in progress in applying this thiiranation to other alkenes.

## ACKNOWLEDGEMENTS

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9. Typical procedures for thiiranaton of **1** with **4** and $Ac_2O$ in a metal−salt solution: To a $Et_2O$ solution of a metal salt (3.0 mL) was added **1** (20.1 mg, 73 μmol) and **4** (17.2 mg, 73 μmol). After the mixture was cooled to −15 °C, $Ac_2O$ (6.8 μL, 73 μmol) was added dropwise to the mixture. After stirring for 45 h at the same temperature, the reaction was quenched by the addition of ice water. After the mixture was diluted with $Et_2O$, the organic layer was separated, washed with $H_2O$ three times, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel and the column was eluted with hexane to give a mixture of **1**, **2**, and **3**, and with $CH_2Cl_2$/hexane (1:5) to give a mixture of oxiranes **5** and **6**. The product ratios were estimated by $^1$H NMR.
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11. **5**: colorless crystals (from $CH_2Cl_2$/MeOH), mp 202.5−203.0 °C; $^1$H NMR (300.1 MHz) $\delta$ 1.01−1.11 (m, 2H), 1.28−1.37 (m, 2H), 1.52−1.73 (m, 9H), 1.85−1.92 (m, 1H), 1.93−2.04 (m, 2H), 2.95−3.03 (m, 2H), 7.10−7.22 (m, 4H); $^{13}$C NMR (50.3 MHz) $\delta$ 25.2, 26.8, 27.1, 34.48, 34.54, 36.5, 36.8, 42.9, 72.1, 86.8, 120.8, 126.9, 144.9; IR (KBr) 3055, 2995, 2976, 2932, 2909, 2846, 1504, 1460, 1446, 1351, 1280, 1238, 1143, 1102, 1066, 1003, 958, 938, 927, 881, 851, 836, 769, 752, 686, 641, 613 cm$^{-1}$; Anal. Calcd for $C_{21}H_{24}N_2O$: C, 86.25; H, 8.27. Found: C, 86.22; H, 8.35. **6**: colorless crystals (from $CH_2Cl_2$/MeOH), mp 198.0−198.5 °C; $^1$H NMR (300.1 MHz) $\delta$ 1.29−1.37 (m, 2H), 1.67−2.06 (m, 14H), 2.11−2.21 (m, 2H), 3.05−3.12 (m, 2H), 7.09−7.17 (m, 2H), 7.18−7.26 (m, 2H); $^{13}$C NMR (50.3 MHz) $\delta$ 25.2, 27.0, 27.3, 33.6, 34.8, 36.7, 37.5, 43.7, 79.2, 79.4, 121.6, 126.1, 145.2; IR (KBr) 3035, 2994, 2946, 2913, 2846, 1446, 1140, 1106, 1011, 957, 924, 837, 757, 728, 642 cm$^{-1}$; Anal. Calcd for $C_{21}H_{24}N_2O$: C, 86.25; H, 8.27. Found: C, 86.01; H, 8.31.
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